Study Protocol

Study Title:	A prospective exploratory study on the value of bio-electrical impedance analysis in IBS.
Study Acronym:	BIA-IBS
Phase of Development:	Exploratory study
Protocol Number:	
Protocol Version and Date:	1.0, December 19th 2021
EudraCT Registry Number:	
ClinicTrials.gov Registry Number:	NCT05744258
Indication:	IBS
Investigational product:	None
Sponsor:	Prof. Dr. Sébastien Kindt
Coordinating/Principal Investigator:	Prof. Dr. Sébastien Kindt

PROTOCOL SIGNATURE PAGE

Protocol Version and date: v1.0, 19 December 2021

Protocol Title: A prospective exploratory study on the value of bio-electrical impedance analysis in IBS.

Sponsor: Prof. Dr. Sébastien Kindt

Principal Investigator: Prof. Dr. Sébastien Kindt

I agree:

- to assume responsibility for the proper conduct of this study
- to conduct the study in compliance with this protocol and any future amendments
- not to implement any deviations from or changes to the protocol without prior review and written approval from the Ethics Committee, except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements)
- that I am thoroughly familiar with the appropriate use of the investigational drug, as described in this protocol
- to ensure that all persons assisting me with the study are adequately informed about the investigational drug and their study-related duties and functions as described in the protocol
- that I am aware of and will comply with the current good clinical practice (GCP) guidelines and ethical principles outlined in the Declaration of Helsinki
- to conduct the study in accordance with all applicable laws and regulations

Printed name Signature Date

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1 Inhoud

2 Trial Registration/Protocol Summary

Information	
EudraCT number: Date of registration:	
Clinical Trial Authorization (CTA) from FAMHP (FAGG) Date of approval:	
ClinicalTrials.gov:	
Official Title:	An prospective exploratory study on the value of bio-electrical impedance analysis in IBS.
Study Phase/Type:	I
Condition:	IBS
Objectives:	The primary objective is to compare the BIA parameters including physical angle (PhA) between IBS and healthy individuals. The secondary objectives are double: - Correlation of PhA with different parameters implicated in IBS pathophysiology in IBS patients and healthy subjects. - Evolution of PhA according to response to therapy.
Investigational Product:	None
Interventions:	Bio-electrical impedance analysis, questionnaires
Endpoints:	The primary endpoint of this study is to explore whether PhA differs between IBS patients and healthy volunteers at visit 1. The secondary endpoints are divided in two parts. The first part explores correlations at initial presentation among IBS patients and healthy subjects: - Correlation of PhA with IPAQ - Multiple regression of IBS status with multiple independent variables (PhA, IPAQ, dietary and FODMAP intake, psychological variables, gender) - Differences in fecal microbiome between groups In the second part, we want to explore changes of PhA according to changes in IBS-SSS in IBS patients only.
Study population:	IBS patients
Number of patients:	20 IBS patients and 20 healthy subjects
Overview of study design:	Prospective exploratory study
Statistical Considerations:	
Sponsor:	Prof. Dr. Sébastien Kindt
Country(ies) of Recruitment:	Belgium
Inclusion Criteria:	IBS patients: - Patients aged 18 - 75 years; - Fulfilling the ROME IV criteria for IBS; For healthy volunteers: - Patients aged 18 - 75 years;
Exclusion Criteria:	- Clinical suspicion of an organic disorder different from IBS (patients can be included when this disorder had been excluded); - Known inflammatory bowel disorder; - Known major intestinal motility disorder;

	- Alcohol (defined as more than 14 U per week) or other substance abuse; - Active psychiatric disorder; - Known systemic or auto-immune disorder with implication for the GI system; - Prior abdominal surgery (with the exception of cholecystectomy or appendectomy); - Any prior diagnosis of cancer other than basocellular carcinoma; - Current chemotherapy; - History of gastro-enteritis in the past 12 weeks; - Dietary supplements unless taken at a stable dose for more than 12 weeks; - Treatment with neuromodulators (one neuromodulator taken at a stable dose for more than 12 weeks is allowed); - Pregnancy.
Date of first enrolment:	
Target sample size:	20 IBS patients and 20 healthy subjects

3 Protocol Version History

Version No.	Approval Date Lead EC	Release Date

4 Sponsor/Coordinating Investigator Information

Coordinating Investigator	Prof. Dr. Sébastien Kindt
Sponsor	
Principal Investigator	Prof. Dr. Sébastien Kindt
Co-investigators	
Additional co-researchers	
Statistician	
Laboratory (ies)	
Pharmacy	
Study Coordinator	Marijke De Wolf - Virgini Van Buggenhout
Study sites and co-investigators	

5 List of Abbreviations

4dFD	Four Day Food Diary
BIA	Bio-electrical Impedance Analysis
FODMAP	Fructo, oligo-, di-, polysacchardies and polyols
HRV	Heart Rate Variability
IBS	Irritable Bowel Syndrome
IBS-SSS	IBS-Symptom Severity Scale
IPAQ	Internation Physical Activity Questionnaire

6 Introduction

6.1 Overview of Disease Pathogenesis

In many aspects, irritable bowel syndrome (IBS) remains a mystery. According to the Rome IV consensus, it is defined as abdominal pain for 3 days a week present since at least 3 months with onset at least 6 months earlier (Lacy 2016). The abdominal pain needs to be associated with two of the following: change in stool form, change in stool frequency or associated with defecation. The aetiology as well as the pathophysiology are uncertain. Studies attribute a role to prior infection, low-grade inflammation, genetic susceptibility, psychological influences and disturbances of the brain-gut axis. As a result of the unclear pathophysiology, a multitude of therapeutic interventions are available, varying from promotion of a healthy lifestyle, dietary modifications, treatments targeting the gut microbiome, antispasmodics, prokinetic or anti-kinetic treatments as well as psychological interventions.

All guidelines recommend lifestyle modifications with increased physical activity, when treating IBS. While the beneficial effects of increased physical exercise have been demonstrated (Johannesson 2011), research on the underlying mechanisms underlying this positive effect remain scarce. Dietary modifications, changes in the gut microbiome (Claus 2021), improved intestinal barrier function (Dalton 2019, Pasini 2019), decreased stress response (Caplin 2021), increased vagal tone (Bonaz 2016), improved mental well-being (Hale 2021, Grocke-Dewey 2021) have been proposed. Further complicating this equation, endurance athletes also report IBS-like symptoms (Killian 2019). However, it remains unknown whether the same pathophysiology is involved as compared to IBS patients with a sedentary lifestyle. Increased intestinal permeability has been implicated.

Apart from the uncertainties about the pathophysiological mechanisms, the absence of an objective marker to diagnose or to follow-up the evolution of IBS represents a major drawback in IBS research. Diagnosis of IBS largely relies on the clinical symptoms and absence of alarm features. No diagnostic test confirms or refutes the diagnosis. Moreover, response to therapy is measured as the improvement of symptoms, which is again susceptible to subjective interpretation by the subject. Current research focuses on different candidate markers (Nakov 2021) such as volatile organic compounds, faecal or serum biomarkers.
Phase Angle (PhA) is a new marker for body cell mass and frailty, derived from Bioelectrical Impedance Analysis (BIA). It has been shown to provide insight into the muscle mass in health and disease at different age (Marini 2012, Rodriguez-Rodriguez 2016, Zanforlini 2019). PhA is considered a potential marker of oxidative and inflammatory processes (da Silva 2022). More recently, its role as a screening tool for physical fitness in obese adults was demonstrated (Streb 2020). Considering the putative role of physical inactivity, dietary factors such as Fructo-, oligo-, di-, polysaccharides and polyols (FODMAP) and low grade inflammation in IBS symptoms as well as physical fitness, PhA might act as a marker for the disease and/ or its evolution during treatment.

6.2 Epidemiology

Up to 5% of the worldwide population suffers from IBS when diagnosed based on the Rome IV criteria. This number increases even more when applying the Rome III criteria, as this diagnosis doesn't restrict the cardinal symptom to abdominal pain, but also allows for abdominal discomfort. On the other hand, a sedentary lifestyle is frequently observed in Western countries. Physical inactivity has been associated with major conditions including obesity, atherosclerosis, non-alcoholic fatty liver disease and diabetes, and might as well be implicated in the pathophysiology of IBS.

6.3 Current Treatments

Current treatment of IBS can be broadly divided into lifestyle modifications, dietary interventions, medical treatment and non-pharmaceutical psychological interventions, including cognitive behavioral therapy. Despite the fact that lifestyle modifications are included in virtually all guidelines, research in the role of physical activity remains underassessed as compared to the other interventions.

6.4 Study Rationale and Purpose

The study aim is to investigate the BIA parameters in general, and PhA in particular in IBS patients and to compare these with values from healthy controls, while assessing the relationship with other confounding parameters in IBS: psychological parameters, physical activity, dietary pattern (with

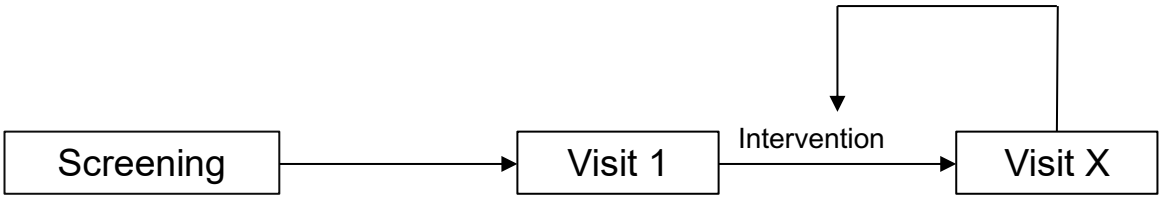
special interest in FODMAP intake). In a second phase, the evolution of the BIA parameters will be analyzed according to response to therapy.

6.5 Rationale for Study Design

The role and significance of bio-electrical impedance analysis has not been studied in IBS. Therefore, we designed this exploratory study to assess its potential role in the diagnosis and follow-up of treatment in IBS.

Study Schematic and Schedule of Activities

6.6 Study Schematic



Screening	Visit 1	Visit X
Inclusion/exclusion ROME IV	BIA IBS-SSS Clinical parameters Psychological questionnaires IPAQ 4dFD	BIA IBS-SSS Clinical parameters IPAQ 4dFD

4dFD Four-day Food Diary
BIA Bio-electrical Impedance Analysis
IBS-SSS IBS-Symptom Severity Scale

6.7 Study Activities

	Screening	Visit 1	Subsequent visits (for patients)
Inclusion/exclusion	X		
Informed consent	X		
Rome IV	X		
Clinical parameters		X	X
Intervention type		X	X
Psychological questionnaires		X	
IPAQ		X	X
Four Day Food Diary		X	X
BIA		X	X
IBS-SSS		X	X

7 Study Objectives and endpoints

7.1 Primary Objective

The primary objective is to compare the BIA parameters including PhA between IBS and healthy individuals.

7.2 Secondary Objectives

The secondary objectives are double:

- Correlation of PhA with different parameters implicated in IBS pathophysiology in IBS patients and healthy subjects.
- Evolution of PhA according to response to therapy.

7.3 Endpoints

The primary endpoint of this study is to explore whether PhA differs between IBS patients and healthy volunteers at visit 1.

The secondary endpoints are multiple and are divided in two parts.
The first part explores correlations at initial presentation among IBS patients and healthy subjects:

- Correlation of PhA with IPAQ
- Multiple regression of IBS status with multiple independent variables (PhA, IPAQ, dietary and FODMAP intake, psychological variables, gender)

In the second part, we want to explore changes of PhA according to changes in IBS-SSS in IBS patients only.

8 Investigational Plan

8.1 Overall Study Design

Explorative non-interventional prospective study. The choice of therapeutic intervention are determined at the discretion of the gastro-enterologist according to standard clinical practice. Several interventions are scheduled in addition to standard clinical practice.

8.2 Study Duration for Subjects

8.2.1 Screening

Screening will last about 15 minutes to check the subject's eligibility either as IBS patient or healthy subject. Informed consent will be obtained.
Eligible subjects will receive instruction on how to fill in the 4dFD. The 4dFD should be filled in during the week following the first visit.

8.2.2 First visit

Participants will be instructed to refrain from eating, drinking and smoking for 6h before attending the first visit. Clinical parameters will be recorded.

During first visit, participants will fill in several questionnaires:

- IBS-SSS
- Psychological parameters:
    - GAD-7
    - PHQ-9
    - PHQ-15
    - VSI
- IPAQ

BIA will be performed.
The first visit will last 30 minutes.

8.2.3 Subsequent visits

Only IBS patients will attend subsequent visits.
The 4dFD should be filled in during the week preceeding the visit.
As much as possible, visits will take place on the same day as the visit to the outpatient clinic. Patients will be instructed to refrain from eating, drinking and smoking for 6h before attending the visit. During these visits the prescribed intervention will be recorded.
During the subsequent visits, IBS patients will fill in several questionnaires:

- IBS-SSS
- IPAQ

BIA will be performed.
Each subsequent visit will last 30 minutes.

8.2.4 Early Study Termination

No early study termination visit is required in this explorative non-interventional study.

8.2.5 End of Study

The study ends when the last study participant quits the study.

9 Selection of Subjects

9.1 Selection of Study Population

IBS patients will be recruited from the outpatient clinic at the Department of Gastroenterology and Hepatology of UZ Brussels. IBS is defined according to ROME IV criteria.
Healthy subjects will be recruited by advertisement.

9.2 Inclusion Criteria

IBS patients:

- Patients aged 18 - 75 years;
- Fulfilling the ROME IV criteria for IBS;

For healthy volunteers:

- Patients aged 18 - 75 years;

9.3 Exclusion Criteria

- Clinical suspicion of an organic disorder different from IBS (patients can be included when this disorder had been excluded);
- Known inflammatory bowel disorder;
- Known major intestinal motility disorder;
- Alcohol (defined as more than 14 U per week) or other substance abuse;
- Active psychiatric disorder;
- Known systemic or auto-immune disorder with implication for the GI system;
- Prior abdominal surgery (with the exception of cholecystectomy or appendectomy);
- Any prior diagnosis of cancer other than basocellular carcinoma;
- Current chemotherapy;
- History of gastro-enteritis in the past 12 weeks;
- Dietary supplements unless taken at a stable dose for more than 12 weeks;
- Treatment with neuromodulators (one neuromodulator taken at a stable dose for more than 12 weeks is allowed);
- Pregnancy.

9.4 Contraception/Pregnancy Avoidance

As no intervention is planned, there is no specific requirement for contraception. However, no further data will be collected from pregnant subjects.

10 Study Assessments and Procedures

10.1 Study Assessments

10.1.1 Screening

At screening a subject's eligibility will be reviewed. Patients should fulfill the ROME IV criteria for IBS. This also includes a physical examination to rule out indications of a possible organic cause for the abdominal symptoms. If another cause of the symptoms is suspected based on history or clinical examination, it should be ruled out before inclusion.
Informed consent will be obtained during the screening visit prior to scheduling study assessments. Instructions about how to fill in the 4DFD will be provided.

10.1.2 First visit

Study participants should be fasting for 6h when attending the first visit.

The 4dFD should be filled in during the week preceding the visit.
Clinical parameters of both IBS patients and healthy subjects will be recorded during the first visit.

During first visit, participants will fill in several questionnaires:
- IBS-SSS
- Psychological parameters:
    - GAD-7
    - PHQ-9
    - PHQ-15
    - VSI
- IPAQ

BIA will be performed.

10.1.3 Subsequent visits

Only IBS patients will attend subsequent visits. They should be fasting for 6h.
The 4dFD should be filled in during the week preceding the visit.
Clinical parameters of IBS patients will be recorded.

During subsequent visits, participants will fill in 2 questionnaires:
- IBS-SSS
- IPAQ

BIA will be performed.

10.2 Assessment Types

10.2.1 Clinical parameters

Body length (cm) will be recorded during the first visit.

Body weight (kg), waist circumference (cm), systolic and diastolic blood pressure (mmHg), heart rate (bpm) will be recorded during each visit. Body mass index will be calculated.

10.2.2 Physical Examination

A physical examination will be performed during each visit in order to exclude a possible organic cause of the abdominal symptoms.

10.2.3 IBS status

Presence of IBS will be established based on the ROME IV criteria (appendix 6). IBS will be sub-typed according to the predominant stool pattern.

10.2.4 Psychological status

Presence of anxiety, depression and somatization will be evaluated by resp. the PHQ-9, the GAD-7 (Spitzer 2006) and PHQ-15 (Kroenke 2002) (appendices 2-4). Gut-directed anxiety will be assessed by the VSI (Labus 2004) (appendix 1). Evaluation of psychological status will be performed during the first visit.

10.2.5 Symptom severity

Symptom severity will be assessed by the IBS-SSS (Francis 1997) during each visit (appendix 7).

10.2.6 Dietary and FODMAP intake

Dietary and FODMAP intake will be evaluated by the 4dFD (appendix 8) at each visit.

10.2.7 Physical activity

Physical activity will be assessed by the International Physical Activity Questionnaire (IPAQ) (Appendix 5).

10.2.8 Bio-electrical Impedance Analysis

Bio-electrical Impedance Analysis will be performed by trained personnel. BIA will be performed after fasting for at least 6 hours. Subjects should refrain from intensive physical activity the day before the measurement. For women, measurements will be performed outside menstruating periods. Subjects will lay down on an examination couch with bare feet. Any jewelry will be removed. Reactance and resistance will be obtained. Phase angle will be calculated according to the formula:

PhA (°) = (reactance/ resistance° x (180°/π).

Body composition, including muscle mass and percentage body fat will be calculated.

11 Data Collection and Management

11.1 Monitoring

The study may be inspected by regulatory authorities, including internal audits from the study center of UZ Brussels. The investigators agree by written consent with this protocol to fully co-operate and support audits and inspections compliance checks by allowing individuals to have access to all the study documentation.

11.2 Data Collection

The investigator will ensure careful entry in the CRF of the clinical data required by the study protocol, checking for concordance with the source documents. The CRF will be filled out in English. Correction to the CRF must be carried out by the investigator or a designated member of the staff. All questions in the CRF should be answered in full. The investigator must provide a reasonable explanation of all missing data.
The CRF will be completed and signed by the investigator.

11.3 Database Management and Quality Control

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the eCRF and in all required reports.
The investigator must keep source documents for each subject in the study. All information on the eCRF must be traceable to these source documents, which are generally stored in the subject's medical file. The source documents should contain all demographic and medical information, including laboratory data, ECGs, etc., and the original signed informed consent forms.
Data reported on the eCRF that derive from source documents should be consistent with the source documents or the discrepancies should be explained.
The investigator and the sponsor should maintain the study documents as specified in the “Essential Documents for the Conduct of a Clinical Trial” chapter 8 of ICH-GCP and as required by the applicable regulatory requirement(s).
These are documents which individually and collectively permit evaluation of a study and the quality of the data produced and include groups of documents, generated before the study commences, during the clinical study, and after termination of the study and include but are not limited to: study protocol, amendments, submission and approval of EC, raw data of subjects including lab tests, insurance contracts, signed informed consent forms, confidential subjects identification code, eCRF, curricula vitae of the investigator and other participants in the study, study staff lists and responsibilities, monitoring reports and final study report.
The investigator and the sponsor should take measures to prevent accidental or premature destruction of these documents.
The investigator and the sponsor must retain study documents as long as needed to comply with ICH-GCP, national and international regulations. By signing the protocol, the investigator and the sponsor agree to adhere to these requirements.

11.4 Statistical Considerations and Data Analysis

In this explorative study assessing the applicability of BIA as a diagnostic modality or tool for objective evaluation of treatment response, 20 IBS subjects and 20 healthy volunteers will be recruited. Based on the results, a larger study will be considered.
Data collection and analysis will be performed by the study team.

12 Ethical Considerations

12.1 Ethical conduct of the study

12.1.1 Declaration of Helsinki

This study will be performed in accordance with the Declaration of Helsinki, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and local laws and regulation as recommended by the European Community.

12.1.2 Ethics Committee

Approval will be obtained from the appropriate regulatory authority in Belgium prior to the start of the study, in this case the Ethical Committee of UZ Brussel. Investigators and personnel are responsible for acting in accordance with their local regulatory requirements.
The study will start on-site only after approval by the local ethical committee.

12.2 Informed Consent

All eligible patients should provide a signed and dated informed consent before inclusion into this study.

12.3 Patient and Study Data Protection

The eCRF will serve as the principal source of data. Source documentation serves to substantiate the integrity of the study data, confirms observations that are recorded and confirms the existence of the study participants.
These data will be checked with adequate precautions to ensure to confidentiality and compliance with applicable data privacy protection laws and regulations. Personnel with responsibilities requiring access to these personal data agree to keep the data confidential.

12.4 Subject Identification

The site will affirm and uphold the principle of the patient's right to protection against the invasion of privacy. Throughout this study and any subsequent data analyses, all data will be identified only by protocol number and ID number.
Only the treating physician will keep the ICF and identity of the patient and healthy subject.

The Data Protection Officer (DPO) will be informed about the database required to perform this study. This included information concerning the goal, the expected number of patients, the type of data that are recorded and the person responsible for the database, according to Belgian regulation.

12.5 Conflict of Interest

All participating investigators will provide written information on possible conflicts of interest upon initiation of the study at their center.

13 Finance and Insurance

Adequate insurance coverage for (i) medical professional and/or malpractice liability and (ii) general liability will be maintained in full force and effect during the term of this study, and following termination of the study to cover any claims arising from the trial.
Additionally in accordance to art. 29 of Belgian Law relating to experiments on human persons, dated May 7th, 2004 an insurance contract will be obtained in order to cover Trial Participants.

14 Reporting and Dissemination

Reporting and dissemination requires prior agreement of the principle investigator.

15 Conflict of interest statement

All participating investigators will provide a list of possible conflicts of interest at the start of the study. This list will be checked every 12 months, and updated if necessary.

16 References

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APPENDIX 1: Visceral Sensitivity Index (VSI) (Labus 2004)

Below are statements that describe how some people respond to symptoms or discomfort in their belly or lower abdomen. These may include pain, diarhoea, constipation, bloating or sense of urgency. Please answer 'how strongly you agree or disagree' with each of these statements, AS THEY RELATE TO YOU. Answer all of the statements as honestly and thoughtfully as you can.

	Strongly agree	Moderately agree	Mildly agree	Mildly disagree	Moderately agree	Strongly disagree
1. I worry that whenever I eat during the day, bloating and distension in my belly will get worse.	1	2	3	4	5	6
2. I get anxious when I go to a new restaurant.	1	2	3	4	5	6
3. I often worry about problems in my belly.	1	2	3	4	5	6
4. I have a difficult time enjoying myself because I cannot get my mind off of discomfort in my belly.	1	2	3	4	5	6
5. I often fear that I won't be able to have a normal bowel movement.	1	2	3	4	5	6
6. Because of fear of developing abdominal discomfort, I seldom try new foods.	1	2	3	4	5	6
7. No matter what I eat, I will probably feel uncomfortable.	1	2	3	4	5	6
8. As soon as I feel abdominal discomfort I begin to worry and feel anxious.	1	2	3	4	5	6
9. When I enter a place I haven't been before, one of the first things I do is look for a bathroom.	1	2	3	4	5	6
10. I am constantly aware of the feelings I have in my belly.	1	2	3	4	5	6
11. I often feel discomfort in my belly could be a sign of a serious illness.	1	2	3	4	5	6

12. As soon as I awake, I worry that I will have discomfort in my bely during the day.	1	2	3	4	5	6
13. When I feel discomfort in my belly, it frightens me.	1	2	3	4	5	6
14. In stressful situations, my belly bothers me a lot.	1	2	3	4	5	6
15. I constantly think about what is happening in my belly.	1	2	3	4	5	6

Appendix 2: General Anxiety Disorder 7 (GAD-7) (Spitzer 2006)

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all	Several days	Over half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all ☐
Somewhat difficult ☐
Very difficult ☐
Extremely difficult ☐

Appendix 3: Patient Health Questionnaire-9 (PHQ-9) (Kroenke 2001)

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself - or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or hurting yourself in some way	0	1	2	3

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all ☐
Somewhat difficult ☐
Very difficult ☐
Extremely difficult ☐

APPENDIX 4: Patient Health Questionnaire-15 (PHQ-15) (Kroenke 2002)

During the past 4 weeks, how much have you been bothered by any of the following problems?	Not bothered at all	Bothered a little	Bothered a lot
1. Stomach pain	0	1	2
2. Back pain	0	1	2
3. Pain in your arms, legs, or joints (knees, hips, etc.)	0	1	2
4. Menstrual cramps or other problems with your periods (women only)	0	1	2
5. Headaches	0	1	2
6. Chest pain	0	1	2
7. Dizziness	0	1	2
8. Fainting spells	0	1	2
9. Feeling your heart pound or race	0	1	2
10. Shortness of breath	0	1	2
11. Pain or problems during sexual intercourse	0	1	2
12. Constipation, loose bowels, or diarrhea	0	1	2
13. Nausea, gas, or indigestion	0	1	2
14. Feeling tired or having low energy	0	1	2
15. Trouble sleeping	0	1	2

Appendix 5: International Physical Activity Questionnaires – Long Form

Part 1 Job-related physical activity

The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home. Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. They are asked in Part 3.

1. Do you currently have a job or do any unpaid work outside your home?
   ☐ Yes
   ☐ No → Skip to part 2: transportation

2. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, heavy construction, or climbing stairs **as part of your work**? Think about only those physical activities that you did for at least 10 minutes at a time.
   _____ days per week
   ☐ No vigorous job-related physical activity → skip to question 4

3. How much time did you usually spend on one of those days doing **vigorous** physical activities as part of your work?
   _____ hours per day
   _____ minutes per day

4. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying loads **as part of your work**? Please do not include walking.
   _____ days per week
   ☐ No moderate job-related physical activity → skip to question 6

5. How much time did you usually spend on one of those days doing **moderate** physical activities as part of your work?
   _____ hours per day
   _____ minutes per day

6. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **as part of your work**? Please do not count any walking you did to travel to or from work.
   _____ days per week
   ☐ No moderate job-related physical activity → skip to part 2: transportation

7. How much time did you usually spend on one of those days **walking** as part of your work?
   _____ hours per day
   _____ minutes per day

Part 2: transportation physical activity

These questions are about how you traveled from place to place, including to places like work, stores, movies and so on.

8. During the **last 7 days**, on how manydays did you **travel in a motor vehicle** like a train, bus, car, or tram?
   _____ days per week
   ☐ No traveling in a motor vehicle → skip to question 10

9. How much time did you usually spend on one of those days **traveling** in a train, bus, car, tram, or other kind of motor vehicle?
   _____ hours per day
   _____ minutes per day

Now think only about the **bicycling** and **walking** you might have done to travel to and from work, to do errands, or to go from place to place.

10. During the **last 7 days**, on how many days did you do **bicycle** for at least 10 minutes at a time to go **from place to place**?
    _____ days per week
    ☐ No bicycling from place to place → skip to question 12

11. How much time do you usually spend on one of those days to **bicycle** from place to place?
    _____ hours per day
    _____ minutes per day

12. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time to go from place to place?
    _____ days per week
    ☐ No walking from place to place → skip to part 3: housework, house maintaining, and caring for family

13. How much time did you usually spend on one of those days **walking** from place to place?
    _____ hours per day
    _____ minutes per day

Part 3: Housework, house maintaining, and caring for family

This section is about some of the physical activities you might have done in the last 7 days in and around your home, like housework, gardening, yard work, general maintenance work, and caring for your family.

14. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, chopping wood, shoveling snow, or digging **in the garden or yard**?
    _____ days per week
    ☐ No vigorous activity in garden or yard → skip to question 16

15. How much time did you usually spend on one of those days doing **vigorous** physical activities in the garden or yard?
    _____ hours per day
    _____ minutes per day

16. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, sweeping, washing windows, and raking **in the garden or yard**?
    _____ days per week
    ☐ No moderate activity in garden or yard → skip to question 18

17. How much time did you usually spend on one of those days doing **moderate** physical activities in the garden or yard?
    _____ hours per day
    _____ minutes per day

18. Once again, think about only those physical activities that you did for at least 10 minutes at a time. During the last days, on how many days did you do moderate activities like carrying light loads, washing windows, scrubbing floors and sweeping inside your home?
    _____ days per week
    ☐ No moderate activity inside home → skip to part 4: recreation, sport and leisure-time physical activity

19. How much time did you usually spend on one of those days doing **moderate** physical activities inside your home?
    _____ hours per day
    _____ minutes per day

Part 4: Recreation, sport, and leisure-time physical activity

This section is about all the physical activities that you did in the **last 7 days** solely for recreation, sport, exercise or leisure. Please do not include any activities you have already mentioned.

20. Not counting any walking you have already mentioned, during the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **in your leisure time**?
    _____ days per week
    ☐ No walking in leisure time → skip to question 22

21. How much time did you usually spend on one of those days walking in your leisure time?
    _____ hours per day
    _____ minutes per day

22. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like aerobics, running, fast bicycling, or fast swimming **in your leisure time**?

_____ days per week
☐ No vigorous activity in leisure time → skip to question 24

23. How much time did you usually spend on one of those days doing **vigorous** physical activities in your leisure time?
_____ hours per day
_____ minutes per day

24. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like bicycling at a regular pace, swimming at a regular pace, and doubles tennis **in your leisure time**?
_____ days per week
☐ No moderate activity in leisure time → skip to part 5: time spent sitting

25. How much time did you usually spend on one of those days doing **moderate** physical activities in your leisure time?
_____ hours per day
_____ minutes per day

Part 5: Time spent sitting

The last questions are about the time you spend sitting while at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down watching television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

26. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekday**?
_____ hours per day
_____ minutes per day

27. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekend day**?
_____ hours per day
_____ minutes per day

APPENDIX 6: ROME IV IBS QUESTIONNAIRE (Dutch version)

Beantwoordt u elke vraag alstublieft zo goed mogelijk, tenzij u wordt verzocht een vraag over te slaan.

1. Hoe vaak had u in de afgelopen 3 maanden pijn ergens in uw buik?
   - Nooit -> Ga naar vraag 6.
   - Minder dan één dag per maand
   - Eén dag per maand
   - Twee tot drie dagen per maand
   - Eén keer per week
   - Twee tot drie dagen per week
   - Bijna elke dag (vier tot zes dagen per week)
   - Elke dag
   - Meerdere keren per dag of constant

2. Hoe vaak kwam deze pijn in uw buik voor rond het moment van de ontlasting - net ervoor, tijdens of kort erna? (Percentage van het totaal aantal keren met pijn)
   - 0 % Nooit
   - 10 %
   - 20 %
   - 30 %
   - 40 %
   - 50 %
   - 60 %
   - 70 %
   - 80 %
   - 90 %
   - 100 % Altijd

3. Hoe vaak was uw ontlasting zachter of harder dan normaal wanneer u deze pijn had? (Percentage van het totaal aantal keren met pijn)
   - 0 % Nooit
   - 10 %
   - 20 %
   - 30 %
   - 40 %
   - 50 %
   - 60 %
   - 70 %
   - 80 %
   - 90 %
   - 100 % Altijd

4. Hoe vaak had u ofwel vaker dan normaal ofwel minder vaak ontlasting dan normaal wanneer u deze pijn had? (Percentage van het totaal aantal keren met pijn)

- 0 % Nooit
- 10 %
- 20 %
- 30 %
- 40 %
- 50 %
- 60 %
- 70 %
- 80 %
- 90 %
- 100 % Altijd

5. Is het 6 maanden of langer dat u deze pijn begon te hebben?

- Nee
- Ja

6. Wanneer u in de afgelopen 3 maanden abnormale ontlasting had, hoe zag het er dan meestal uit?

- Meestal constipatie (zoals type 1 of 2 in de afbeelding)
- Meestal diarree (zoals type 6 of 7)
- Zowel diarree als constipatie, dat wil zeggen: meer dan ¼ van de abnormale ontlasting was constipatie en meer dan ¼ was diarree

Niet van toepassing, omdat ik zelden of nooit abnormale ontlasting had

APPENDIX 7: IBS Symptom Severity Scale (IBS-SSS) (Dutch version)

1a. Hebt u in de afgelopen 10 dagen last gehad van buikpijn/maagpijn?

- ❍ Nee → **Ga naar vraag 3a**
- ❍ Ja

1b. Hoe hevig was uw buikpijn/maagpijn in de afgelopen 10 dagen?
(Geef een getal aan van 0 tot 100, waarbij 0 'geen pijn' betekent en 100 'heel hevige pijn')

- ❍ 0 Geen pijn
- ❍ 10
- ❍ 20
- ❍ 30
- ❍ 40
- ❍ 50
- ❍ 60
- ❍ 70
- ❍ 80
- ❍ 90
- ❍ 100 Heel hevige pijn

2. Geef aan hoeveel dagen u van de afgelopen 10 dagen buikpijn heeft gehad.
(Als u bijvoorbeeld 4 aangeeft, heeft u 4 van de 10 dagen pijn gehad) Als u elke dag pijn had, voer dan 10 in).

- ❍ 0 dagen
- ❍ 1
- ❍ 2
- ❍ 3
- ❍ 4
- ❍ 5
- ❍ 6
- ❍ 7
- ❍ 8
- ❍ 9
- ❍ 10 dagen

3a. Hebt u de afgelopen 10 dagen last gehad van een opgezette buik (opgeblazen, gezwollen of gespannen buik of maagstreek)?
Vrouwen: Tel opgezetheid vanwege uw menstruatie niet mee wanneer u deze vraag beantwoordt.

- ❍ Nee → **Ga naar vraag 4**
- ❍ Ja

3b. Hoe erg was uw opgezette/gespannen buik in de afgelopen 10 dagen?
(Geef een getal aan van 0 tot 100, waarbij 0 'niet opgezet' betekent en 100 'heel hevig opgezet')

- ❍ 0 -- niet opgezet
- ❍ 10
- ❍ 20
- ❍ 30
- ❍ 40
- ❍ 50
- ❍ 60
- ❍ 70
- ❍ 80
- ❍ 90
- ❍ 100 -- heel hevig opgezet

4. Hoe ontevreden bent u over het functioneren van uw darmen in de afgelopen 10 dagen?
(Geef een getal aan van 0 tot 100, waarbij 0 ‘niet ontevreden’ betekent en 100 ‘heel ontevreden’)

- ❍ 0 -- niet ontevreden
- ❍ 10
- ❍ 20
- ❍ 30
- ❍ 40
- ❍ 50
- ❍ 60
- ❍ 70
- ❍ 80
- ❍ 90
- ❍ 100 -- heel ontevreden

5. Hoe erg heeft de buikpijn of het ongemak in uw buik of het anders functioneren van uw darmen uw leven in het algemeen beïnvloed of belemmerd in de afgelopen 10 dagen?
(Geef een getal aan van 0 tot 100, waarbij 0 ‘helemaal niet’ betekent en 100 ‘volledig’)

- ❍ 0 -- helemaal niet
- ❍ 10
- ❍ 20
- ❍ 30
- ❍ 40
- ❍ 50
- ❍ 60
- ❍ 70
- ❍ 80
- ❍ 90
- ❍ 100 -- volledig

Appendix 8: Four Day Food Diary example (Dutch version)

4-daags voedingsdagboek

Het voedingsdagboek zal ons helpen om een inzicht te krijgen in uw voedingspatroon. Schrijf daarom gedurende 4 dagen op wat u precies eet en drinkt, kies 3 weekdagen en 1 weekenddag. Eet en drink gedurende deze dagen zo normaal mogelijk, vermijd geen voedingsmiddelen en ga ook niet ineens anders eten dan gewoonlijk.

Bekijk het voorbeeld op de volgende pagina.

Schrijf meteen alles op, direct opschrijven voorkomt dat u dingen zou vergeten. U neemt het voedingsdagboek dus best overal mee gedurende deze 4 dagen.

Noteer zo duidelijk mogelijk op hetgeen u eet of drinkt : hoeveelheid (portiegrootte of gewicht) is belangrijk maar ook zoveel mogelijk info over de voeding zelf (bv wit of grijs brood, volle of halfvolle melk, gewone of light frisdrank, ….) U mag zeker ook merknamen vermelden of een etiket toevoegen.

Vergeet ook niet snacks en drankjes tussendoor te vermelden.

Voorbeelddag

Tijdstip	wat gegeten/gedronken	hoeveelheid
ontbijt	granola (Dr Oetker)	30 g
	Halfvolle natuuryoghurt	1 potje van 125 g
	Koffie met halfvolle melk en zoetstof	1 tas, scheutje melk, 1tablet zoetstof
tussendoor	banaan	1 volledige
	Water	1 glas
middag	meergranenbrood	4 sneden van een groot rond brood
	Minarine	dun gesmeerd
	Light smeerkaas	2 driehoekjes
	Salami	2 sneetjes
	Groentesoep	1 grote soepbol
	Cola light	1 blikje 330 ml
tussendoor	suikerwafel met chocolade (Suzy)	55g (kijk op verpakking)
	Thee citroen	1 tas
avondmaal	blinde vink	1 stuk
	Bloemkool in bechamel	1/3 van het bord, bechamelsaus bereid met half-Volle melk
	Natuuraardappelen	3 stuks grootte van een ei
	Margarine voor bakken en braden	2 eetlepels voor maaltijd 4 personen
	Rode wijn	1 glas
tussendoor	vanillepudding bereid met halfvolle melk en suiker	dessertschaaltje